

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>11137/04702</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 02366</b>	International filing date (day/month/year) <b>28/01/2000</b>	(Earliest) Priority Date (day/month/year) <b>29/01/1999</b>
Applicant  <b>THE SAMUEL ROBERTS NOBLE FOUNDATION, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

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☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PC 00/02366

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/82 C12N9/10 C07K14/415 A23L1/29 A23K1/165  
 A61K38/45 A61K31/05 A01H5/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A23L A23K A61K A01H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS 'Online!            BIOSCIENCES INFORMATION SERVICE,            PHILADELPHIA, PA, US; 1994            WATERHOUSE ANDREW L ET AL: "The occurrence            of piceid, a stilbene glucoside, in grape            berries."            Database accession no. PREV199598011522            XP002140721            abstract            &amp; PHYTOCHEMISTRY (OXFORD),            vol. 37, no. 2, 1994, pages 571-573,            ISSN: 0031-9422</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1,6,11,            16,21,            34,47</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

4 July 2000

Date of mailing of the international search report

17/07/2000

Name and mailing address of the ISA

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Authorized officer

Maddox, A

## INTERNATIONAL SEARCH REPORT

International Application No

P 00/02366

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 198637  Derwent Publications Ltd., London, GB;  Class B04, AN 1986-242358  XP002140790  &amp; JP 61 171427 A (OSAKA YAKUHI KENKYUSHO  KK), 2 August 1986 (1986-08-02)  abstract</p> <p>---</p>	<p>1,6,  16-20,  34,35,  51,53</p>
X	<p>SOLEAS G J ET AL: "RESVERATROL: A  MOLECULE WHOSE TIME HAS COME? AND GONE?"  CLINICAL BIOCHEMISTRY, XX, PERGAMON PRESS,  vol. 30, no. 2, March 1997 (1997-03),  pages 91-113, XP000856542  ISSN: 0009-9120  the whole document</p> <p>---</p>	<p>16-20,  34,35,  51,53</p>
X	<p>EP 0 773 020 A (SIGMA TAU IND FARMACEUTI)  14 May 1997 (1997-05-14)</p> <p>the whole document</p> <p>---</p>	<p>16-20,  34,35,  51,53</p>
X	<p>WANG Z -Z ET AL: "REDUCING EFFECT OF  3,4',5-TRIHYDROXYSTIBENE-3-BETA-MONO-D-  GLUCOSIDE ON ARTERIAL THROMBOSIS INDUCED  BY VASCULAR ENDOTHELIAL INJURY"  ZHONGUA YAOLI XUEBAO - ACTA PHARMACOLOGICA  SINICA, CN, SHANGHAI,  vol. 16, no. 2, 1 March 1995 (1995-03-01),  pages 159-162, XP002042342  ISSN: 0253-9756  the whole document</p> <p>---</p>	<p>16-20,  35,51,53</p>
X	<p>ZHANG P -W ET AL: "INFLUENCE OF  3,4',5-TRIHYDROXYSTIBENE-3-BETA-MONO-D-GLU  COSIDE ON VASCULAR ENDOTHELIAL  EPOPROSTENOL AND PLATELET AGGREGATION"  ZHONGUA YAOLI XUEBAO - ACTA PHARMACOLOGICA  SINICA, CN, SHANGHAI,  vol. 16, no. 3, 1 May 1995 (1995-05-01),  pages 265-268, XP002042343  ISSN: 0253-9756  the whole document</p> <p>---</p>	<p>16-20,  35,51,53</p>
X	<p>ORSINI, F., ET AL.: "Isolation,  synthesis, and antiplatelet aggregation  activity of resveratrol  3-O-beta-D-glucopyranoside and related  compounds"  JOURNAL OF NATURAL PRODUCTS,  vol. 60, no. 11, November 1997 (1997-11),  pages 1082-1087, XP000914920  the whole document</p> <p>---</p>	<p>16-20,  35,51,53</p>

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## INTERNATIONAL SEARCH REPORT

International Application No

P S 00/02366

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JAYATILAKE GAMINI S ET AL: "Kinase inhibitors from Polygonum cuspidatum." JOURNAL OF NATURAL PRODUCTS (LLOYDIA), vol. 56, no. 10, 1993, pages 1805-1810, XP000914921 ISSN: 0163-3864 the whole document	16-20, 35,51,53
X	--- JANG M ET AL: "CANCER CHEMOPREVENTIVE ACTIVITY OF RESVERATROL, A NATURAL PRODUCT DERIVED FROM GRAPES" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 275, 10 January 1997 (1997-01-10), pages 218-220, XP000857972 ISSN: 0036-8075 the whole document	35,51,53
X	--- GB 2 317 561 A (HOWARD FOUNDATION) 1 April 1998 (1998-04-01) page 3, paragraph 3	35
X	--- LECKBAND G ET AL: "Transformation and expression of a stilbene synthase gene of Vitis vinifera L. in barley and wheat for increased fungal resistance." THEORETICAL AND APPLIED GENETICS, vol. 96, no. 8, June 1998 (1998-06), pages 1004-1012, XP000923027 ISSN: 0040-5752 the whole document	21-28, 37-39, 43,44, 47-50
X	--- DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; October 1997 (1997-10) THOMZIK J E ET AL: "Synthesis of a grapevine phytoalexin in transgenic tomatoes (Lycopersicon esculentum Mill.) conditions resistance against Phytophthora infestans." Database accession no. PREV199800171398 XP002140722 abstract & PHYSIOLOGICAL AND MOLECULAR PLANT PATHOLOGY, vol. 51, no. 4, October 1997 (1997-10), pages 265-278, ISSN: 0885-5765	21-28, 37-39, 43,44, 47-50
X	--- EP 0 309 862 A (BAYER AG) 5 April 1989 (1989-04-05)  the whole document	21-28, 37-39, 43,44, 47-50
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## INTERNATIONAL SEARCH REPORT

International Application No

P S 00/02366

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FISCHER REGINA ET AL: "Stilbene synthase gene expression causes changes in flower colour and male sterility in tobacco." PLANT JOURNAL, vol. 11, no. 3, 1997, pages 489-498, XP002140720 ISSN: 0960-7412 the whole document ---	37-39
X	FISCHER R: "OPTIMIERUNG DER HETEROLOGEN EXPRESSION VON STILBENSYNTHASEGENEN FUER DEN PFLANZENSCHUTZ" DISSERTATION, UNIVERSITY OF HOHNEHEIM, DECEMBER 1994, 1 December 1994 (1994-12-01), pages 1-158, XP002081885 the whole document ---	37-39
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 GOLDBERG DAVID M ET AL: "Resveratrol glucosides are important components of commercial wines." Database accession no. PREV199799334030 XP002140723 abstract & AMERICAN JOURNAL OF ENOLOGY AND VITICULTURE, vol. 47, no. 4, 1996, pages 415-420, ISSN: 0002-9254 -----	51,53

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P S 00/02366

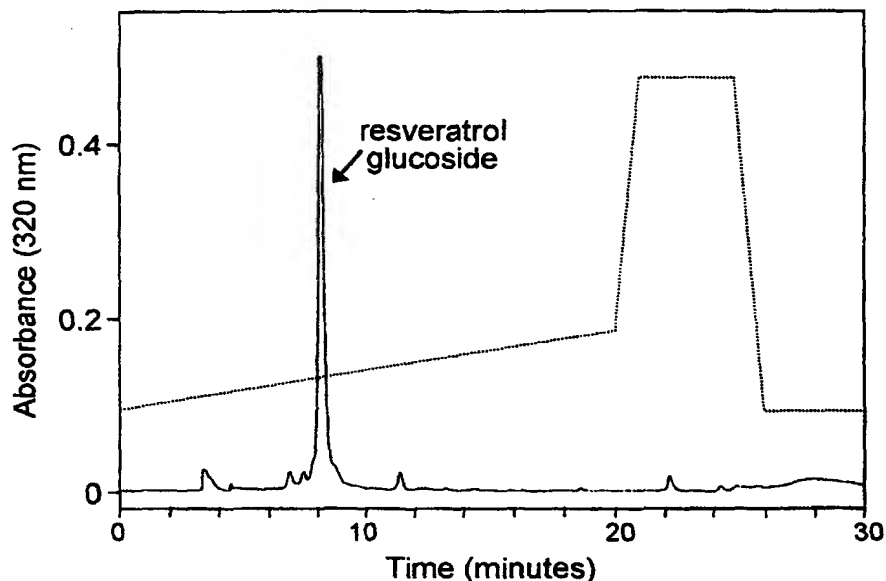
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 61171427 A	02-08-1986	JP 1810047 C	27-12-1993
		JP 5016413 B	04-03-1993
EP 0773020 A	14-05-1997	IT RM950687 A	17-04-1997
		CA 2187990 A	18-04-1997
		JP 9165331 A	24-06-1997
		US 5747536 A	05-05-1998
GB 2317561 A	01-04-1998	AU 4310597 A	14-04-1998
		AU 4310697 A	14-04-1998
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		CZ 9900973 A	11-08-1999
		EP 0930831 A	28-07-1999
		WO 9811789 A	26-03-1998
		WO 9812189 A	26-03-1998
		GB 2317889 A	08-04-1998
		NO 991351 A	19-05-1999
		PL 332306 A	30-08-1999
		PL 332312 A	30-08-1999
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EP 0309862 A	05-04-1989	DE 3733017 A	13-04-1989
		DE 3873672 A	17-09-1992
		JP 1101888 A	19-04-1989
		JP 2812685 B	22-10-1998
		US 5689046 A	18-11-1997
		US 6020129 A	01-02-2000
		US 5985647 A	16-11-1999



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>C12N 15/82, 9/10, C07K 14/415, A23L 1/29, A23K 1/165, A61K 38/45, 31/05, A01H 5/00</b>		<b>A1</b>	(11) International Publication Number: <b>WO 00/44921</b>
			(43) International Publication Date: 3 August 2000 (03.08.00)
(21) International Application Number: PCT/US00/02366		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 28 January 2000 (28.01.00)		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(30) Priority Data: 60/117,888 29 January 1999 (29.01.99) US			
(71) Applicant (for all designated States except US): THE SAMUEL ROBERTS NOBLE FOUNDATION, INC. [US/US]; 2510 Sam Noble Parkway, Ardmore, OK 73402 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): HIPSKIND, John, D. [US/US]; 113 Brampton Ln., Apt #1D, Cary, NC 27513 (US). PAIVA, Nancy, L. [US/US]; HCR 70, Box 100, Ardmore, OK 73401 (US).			
(74) Agents: HANSEN, Eugenia, S. et al.; Sidley & Austin, Suite 3400, 717 N. Harwood, Dallas, TX 75201 (US).			

(54) Title: TRANSGENIC PLANTS MODIFIED TO CONTAIN RESVERATROL GLUCOSIDE AND USES THEREOF



## (57) Abstract

Heterologous plants that otherwise do not produce stilbenes and do not, therefore, enjoy the benefits of stilbenes, have been transformed to produce high levels of resveratrol glucoside. Such transgenic plants or plant cells can be utilized directly or in preparation of compositions suitable for administration as a food, a nutritional supplement, an animal feed supplement, a nutraceutical, or a pharmaceutical to provide nutritional or therapeutic benefit.

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 11137/04702		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/02366	International filing date (day/month/year) 28/01/2000	Priority date (day/month/year) 29/01/1999
International Patent Classification (IPC) or national classification and IPC C12N15/82		
Applicant THE SAMUEL ROBERTS NOBLE FOUNDATION, INC. et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 8 sheets, including this cover sheet.  
  
☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of 6 sheets.

- This report contains indications relating to the following items:
  - ☒ Basis of the report
  - ☐ Priority
  - ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - ☐ Lack of unity of invention
  - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - ☐ Certain documents cited
  - ☐ Certain defects in the international application
  - ☒ Certain observations on the international application

Date of submission of the demand  25/08/2000	Date of completion of this report  18.05.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Marinoni, J-C  Telephone No. +49 89 2399 8563  



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/02366

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-36 as originally filed

**Claims, No.:**

1-57 with telefax of 09/04/2001

**Drawings, sheets:**

1/19-19/19 as originally filed

**Sequence listing part of the description, pages:**

1-6, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/02366

- ☐ the description,      pages:  
☐ the claims,      Nos.:  
☐ the drawings,      sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

**see separate sheet**

6. Additional observations, if necessary:

**see separate sheet**

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	1-30, 32-57
	No:	Claims	None
Inventive step (IS)	Yes:	Claims	1-30, 32-57
	No:	Claims	None
Industrial applicability (IA)	Yes:	Claims	1-30, 32-57
	No:	Claims	None

### 2. Citations and explanations

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item I**

**Basis of the report**

1. At least some of the amendments introduced with the fax dated 09 April 2001 do not comply with the requirements of Article 34(2) PCT.
2. These amendments concern
  - (i) the addition to the wording of **claims 27, 34 and 41** of the sentence "cultivating said transgenic plant cell under conditions conducive to regeneration and plant growth and under conditions conducive to the accumulation of p-coumaryl CoA and malonyl CoA precursors and the suppression of  $\beta$ -glucosidases".
  - (ii) the filing of new **claim 31** that comprises the same sentence and which subject-matter is directed to a method to produce isolated resveratrol glucoside.
3. Although it is clear from the description that p-coumaryl CoA and malonyl CoA are necessary to the biosynthesis of resveratrol, the application as originally filed does not indicate nor suggest such culture conditions of the transgenic plant cells. The addition of said feature has therefore no basis in the application.  
As a consequence, the opinion on **claims 27, 34 and 41** is given as if this feature was not present in the claims.
4. Nothing in the application as originally filed concerns such a method to produce isolated (*i.e.* to purify) resveratrol glucoside from transgenic plants. No opinion is given on the subject-matter of presently filed **claim 31**.

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:  
**D1:** DATABASE BIOSCIENCES INFORMATION SERVICE, Andrew et al. 'The occurrence of piceid, a stilbene glucoside, in grape berries.' Database accession no. PREV199598011522 & PHYTOCHEMISTRY, Vol. 37, No. 2,

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/02366

- 1994, pages 571-573
- D2:** EP 0 309 862, 5 April 1989
- D3:** THEOR. APPL. GENET., Vol. 96, No. 8, June 1998, pages 1004-1012,  
Leckband et al. 'Transformation and expression of a stilbene synthase gene  
of *Vitis vinifera* L. in barley and wheat for increased fungal resistance'
- D4:** DATABASE BIOSCIENCES INFORMATION SERVICE, October 1997  
Thomzik et al. 'Synthesis of a grapevine phytoalexin in transgenic tomatoes  
(*Lycopersicon esculentum* Mill.) conditions resistance against *Phytophthora  
infestans*' Database accession no. PREV199800171398 & PHYSIOL.  
MOLEC. PLANT PATH., Vol. 51, No. 4, October 1997, pages 265-278
- D5:** EP 0 773 020, 14 May 1997
- D6:** DATABASE BIOSCIENCES INFORMATION SERVICE, 1996, Goldberg et  
al. 'Resveratrol glucosides are important components of commercial wines.'  
Database accession no. PREV199799334030 & AM. J. ENOL. VITIC., Vol.  
47, No. 4, 1996, pages 415-420
- D7:** SCIENCE, Vol. 275, pages 218-220, 10 January 1997, Jang et al. 'Cancer  
chemopreventive activity of resveratrol, a natural product derived from  
grapes'
- D8:** DATABASE WPI Section Ch, Week 198637 Derwent Publications Ltd.;  
Class B04, AN 1986-242358 & JP 61 171427 A, 2 August 1986
- D9:** CLIN. BIOCHEM., Vol. 30, No. 2, March 1997, pages 91-113, Soleas et al.  
'Resverateol: a molecule whose time has come? and gone?'
- D10:** ZHONGUA YAOLI XUEBAO - ACTA PHARMACOLOGICA SINICA, Vol. 16,  
No. 2, 1 March 1995, pages 159-162, Wang et al. 'Reducing effect of 3,4',5-  
trihydroxystiben-3- $\beta$ -mono-D-glucoside on arterial thrombosis induced by  
vascular endothelial injury'
- D11:** ZHONGUA YAOLI XUEBAO - ACTA PHARMACOLOGICA SINICA, Vol. 16,  
No. 3, 1 May 1995, pages 265-268, Zhang et al. 'Influence of 3,4',5-  
trihydroxystiben-3- $\beta$ -mono-D-glucoside on vascular endothelial  
epoprostenol and platelet aggregation'
- D12:** J. NAT. PROD., Vol. 60, No. 11, November 1997, pages 1082-1087, Orsini  
et al. 'Isolation, synthesis, and antiplatelet aggregation activity of resveratrol  
3-O- $\beta$ -D-glucopyranoside and related compounds'
- D13:** Fischer 'Optimierung der heterologen expression von stilbensynthasegenen  
für den pflanzenschutz', Dissertation, Univ. Hohenheim, 1 December 1994,

pages 1-158

2. It is considered that the terms "resveratrol synthase" (used in the application) and "stilbene synthase" (commonly used in the cited prior art) designate the same enzyme (see **D2**, claim 2; **D12**, page 96, the sentence linking the left and the right column; **D13**, page 9, lines 7-8).

3. **Claim 1** is directed to an edible plant material comprising transgenic plant cells, transformed with a resveratrol synthase transgene under the control of a constitutive promoter.

The subject-matter of **claim 1** meets the requirements of Article 33(2) PCT concerning novelty. However, the objection raised under **item VIII-1** should be taken into consideration.

**D2** describes a transgenic alfalfa (see example/item 4) and potatoes (see example/item 5), *i.e.* edible plant material comprising transgenic plant cells, wherein the gene encoding resveratrol synthase from *Arachis hypogea* (peanut) has been introduced. However, the expression of the gene does not appear to be constitutive.

**D3** describes transgenic wheat and barley, *i.e.* edible plant material comprising transgenic plant cells, wherein a gene encoding resveratrol synthases from *Vitis vinifera* (grapevine) has been introduced under the control of the *Vst1* promoter (not constitutive).

**D4** describes transgenic tomatoes, *i.e.* an edible plant material comprising transgenic plant cells, wherein two genes encoding resveratrol synthases from *Vitis vinifera* (grapevine) apparently under the control of their own non-constitutive promoters have been introduced.

**D13** describes transgenic tobacco which has been transformed with two different stilbene synthase genes (*Vst1* from vine or *PSS* from pine) under the control of inducible (*Vst1*) or constitutive *CaMV35SmRNA* promoters. However, tobacco cannot be considered as an edible plant (the objection under **Item VIII-2** should be taken into consideration).

6. The claims are considered to meet the requirements of Article 33(3) PCT concerning inventive step. However, the objection under **Item VIII-3** should be taken into consideration.

**Re Item VIII**

**Certain observations on the international application**

1. The word "transgenic" is meaningless *per se*. Although it indicates the process by which the plant has been obtained (see the Guidelines, Ch. III, 4.5), it does not provide sufficient information to distinguish the plant thereby obtained from the plants which in nature comprise said gene. Moreover, the term "transgenic" does not necessarily mean that (i) the plant does not "naturally" contain a functional resveratrol synthase gene, or that (ii) the gene originates from another organism than the plant. In the present wording, the claimed plant is not distinguishable from a plant that would "naturally" comprise the resveratrol synthase gene under the control of a constitutive promoter. It is considered that said plant exists and that "in some plant species, resveratrol production is inducible" (see 2, lines 23-24; page 1, lines 18-21 of the present application).
2. The claims are directed to "edible plant material comprising transgenic plant cells". The term "edible plant material" is not sufficiently clear to define precisely what is claimed. Although tobacco cannot be considered edible *per se*, (parts of) it could be used as part of, for instance, animal diet (*i.e.* an edible plant material). The subject-matter of **claim 1** is therefore not clear (Article 6 PCT).
3. An inventive step can only be acknowledged for the plants for which support of technical character can be found in the description (*i.e.* alfalfa and soybean), since *a priori*, nothing in the prior art nor in the present application would hint the skilled person to select another plant than soybean that would have the property of accumulating resveratrol glucoside upon transformation with the gene encoding resveratrol synthase since it appears (i) that not all plants have this property and (ii) that not all plants having this property are known: consequently, the subject-matter of the present claims cannot be put into practice over the entire range claimed (Articles 5 and 6 PCT).

4. None of the available documents pertaining to the transformation of plants with resveratrol (or stilbene) synthase mentions the production of resveratrol glucoside. Although it is understood that some conditions are required for the production of resveratrol glucoside (*inter alia* the activity of the endogenous glucosyl transferase), it is however not clear whether some at least of the plants mentioned in these documents are indeed capable of synthesising this product (see **item VIII-3**). It may be that upon transformation with a gene encoding resveratrol synthase, the edible transgenic plants disclosed in the available documents produce resveratrol glucoside. Combined with the fact that tobacco (non edible plant) has already been transformed with a resveratrol synthase gene under the control of a constitutive promoter, inventive step could be questioned in the regional phase of the procedure.

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C. 20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 03 October 2000 (03.10.00)	
<b>International application No.</b> PCT/US00/02366	<b>Applicant's or agent's file reference</b> 11137/04702
<b>International filing date</b> (day/month/year) 28 January 2000 (28.01.00)	<b>Priority date</b> (day/month/year) 29 January 1999 (29.01.99)
<b>Applicant</b> HIPSKIND, John, D. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

25 August 2000 (25.08.00)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Pascal Piriou  Telephone No.: (41-22) 338.83.38
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